

REVIEW article

Molecular insights into the oxidative stress-inflammation nexus: Review on the mechanisms and consequences for human health

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Abstract: The maintenance of physiological homeostasis is a crucial player for healthy living. Oxidative stress and inflammation are tightly linked biological processes that play central roles in maintaining this balance. Oxidative stress is a consequence of an imbalance between reactive species (ROS/RNS) production and the body's antioxidant defense systems, leading to oxidative damage to body macromolecules, including lipids, proteins, and DNA. On the other hand, inflammatory responses are initiated through pattern recognition receptors (PRRs) that detect pathogenic and damage-associated signals, activating signaling pathways including NF- κ B and MAPK pathways. Emerging evidence describes a bidirectional relationship in which excessive ROS amplifies inflammatory signaling, while activated immune cells further enhance oxidative stress, creating a self-perpetuating cycle. Key signaling molecules, such as HMGB1 and the NLRP3 inflammasome, mediate redox imbalance to cytokine production and immune activation. The oxidative stress-inflammation nexus is a major contributor to the pathophysiology of various disorders, including cardiovascular, neurodegenerative, and metabolic diseases. Therapeutic interventions designed to target this interplay may represent a promising strategy for the treatment of diseases associated with oxidative stress-linked inflammatory responses.

Introduction

One of the major determinants of healthy living is the maintenance of homeostatic equilibrium within the physiological systems in the human body. This includes energy homeostasis, pH regulation, osmotic and electrolyte balance as well as hormonal stability [1]. Additionally, two other critical components of homeostasis that contribute to overall health are oxidative balance and the regulation of inflammatory responses. Free radicals are molecules possessing one or more unpaired electrons, which make them highly reactive and short-lived. These species are naturally generated as by-products of cellular metabolic processes such as the electron transport chain in the mitochondrial matrix. In a normo-physiological state, the body's antioxidant systems eliminate free radicals at a rate that maintains equilibrium, thus ensuring balance between the generation and neutralization of free radicals in the system [2]. Although (at low concentration) free radicals are known to play beneficial roles, including the modulation of signaling pathways and detoxification of xenobiotics. A quantitative leap in the production of free radicals that surpasses the capacity of the body's antioxidant defense system will ultimately lead to oxidative stress. This imbalance directly triggers several

cellular reactions leading to cellular damage, particularly to polyunsaturated fatty acids in biological membranes. During oxidative attacks, these lipids are converted to reactive peroxides that initiate chain reactions, leading to membrane dysfunction [3]. The resulting impairment of cellular membranes compromises their structural and functional integrity, contributing to a cascade of detrimental effects on tissues and cellular systems.

Inflammation is a conserved defense mechanism by which the body responds to infections, toxins, or injuries. This response is tightly regulated by two classes of cytokines: Pro-inflammatory cytokines, which promote inflammation and immune defense, and anti-inflammatory cytokines, which palliate excessive inflammatory activity [3, 4]. The dynamic homeostasis between these cytokines is imperative to ensure effective immune responses without inflicting damage on healthy tissues [5]. Chronic inflammation arises when pro-inflammatory cytokines are persistently overexpressed, leading to protracted inflammatory states. This persistent inflammation can damage tissues and disrupt normal physiological functions, laying the foundation for various pathological conditions [6]. The interaction between oxidative stress and chronic inflammation is a significant driver of numerous human disorders. Oxidative stress aggravates inflammatory responses by activating pathways that amplify pro-inflammatory cytokine production [7]. Chronic inflammation, on the other hand, can amplify oxidative stress through the generation of reactive oxygen species by the activated immune cells. This mutual reinforcement ultimately creates a vicious cycle that contributes to the pathogenesis and progression of various disorders [8]. In this review, we will explore recent scientific literature for possible molecular mechanisms involved in the crosslinks between oxidative stress and chronic inflammation as well as their combined impact on human health.

Oxidative stress: Mechanisms and biological significance

The concept of oxidative stress has evolved; it was formerly defined only as the imbalance between oxidant and antioxidant levels of the system. The recent definition has brought a more comprehensive understanding to incorporate specific factors and clarity. Oxidative stress is generally referred to as the state of imbalance between the production of oxidants or reactive species and the ability of the body to neutralize them with antioxidants, in favor of the oxidants, leading to disturbance in redox signaling and molecular damage [9]. Reactive species are produced physiologically as by-products of energy metabolism in a regulated manner, so maintaining a threshold. At this threshold, they serve different physiological roles in the system, including redox homeostasis, chemotaxis, apoptosis, and cell adhesion [10]. A problem arises when their production or availability exceeds the body's regulatory mechanisms, as accepted by the body's antioxidant systems.

Interestingly, studies have unraveled the two primary sources (**Figure 1**) of reactive species exposure to living systems. One of the major sources, which may even be the real initiator of imbalance, is external sources, which include environmental factors such as the effluent of industrial processes, tobacco smoke, ionizing radiation, as well as certain drugs [11]. The endogenous sources of free radical generation involved mitochondrial, peroxisomes, endoplasmic reticulum, as well as the cytosol. The electron leakage at complex I, II, and III during the energy-generating process within the mitochondrial (electron transport chain) ultimately generates superoxide radicals through one-electron reduction of molecular oxygen [12, 13]. Microbodies (peroxisomes) produce hydrogen peroxide through the action of acyl-CoA oxidases during β -oxidation. At the same time, drug-metabolizing enzymes in the endoplasmic reticulum, particularly those of the cytochrome P450 family (CYPs), also contribute to intracellular free radical generation. Several studies have pinned this generation to the heme-dependent redox cycling and reaction uncoupling nature of CYP-metabolized reactions, leading to the formation of ROS as well as reactive intermediates such as N-acetyl-p-benzoquinone imine (NAPQI) [14, 15]. The endoplasmic reticulum can also contribute to ROS generation through the protein disulfide isomerase (PDI)- endoplasmic oxidoreduction 1 (Ero1) oxidative protein folding system [16, 17]. A posttranslational process characterized by electron transfer from cysteine residues in newly

synthesized proteins, creating disulfide linkages, reducing PDI, and releasing superoxide anion radicals as a by-product. Moreover, NADPH oxidases (NOX family, notably NOX1-5 and DUOX1/2) generate ROS at the plasma membrane and within endosomes, where they play a role in the regulation of the localized signaling microdomains [18].

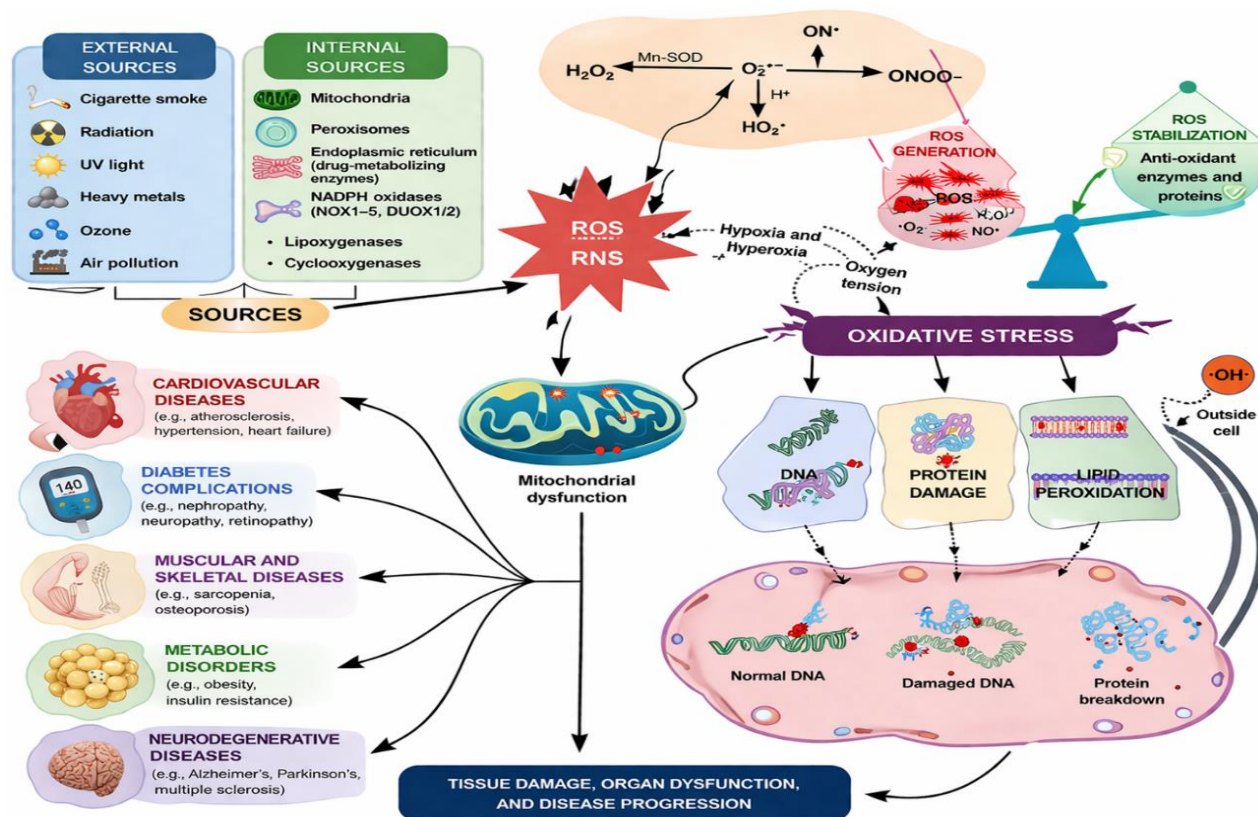


Figure 1: The complex cellular and molecular pathways associated with oxidative stress in various disorders [8]

Reactive oxygen and nitrogen species (ROS/RNS) arise from external exposures (smoke, radiation, pollutants, heavy metals) and internal sources (mitochondria, peroxisomes, ER, NADPH oxidases, etc). Imbalance between ROS generation and antioxidant defenses (e.g., SOD and related enzymes) leads to oxidative stress, promoting mitochondrial dysfunction and macromolecular damage, including DNA lesions, protein oxidation, and lipid peroxidation. These processes culminate in cellular injury and are implicated in the pathogenesis of cardiovascular, metabolic, neurodegenerative, and musculoskeletal diseases, ultimately driving tissue damage, organ dysfunction, and disease progression.

The antioxidant systems are a network of factors responsible for neutralizing free radicals in the system. The system is generally categorized as exogenous and endogenous antioxidants; the exogenous ones are usually gotten from diet and other supplements (including tocopherols, retinols, calciferols, etc.). Endogenous antioxidants are innate factors inbuilt naturally within the body system; they are further grouped into enzymatic (e.g., catalase, superoxide dismutase, glutathione peroxidase) and non-enzymatic systems (glutathione, bilirubin, vitamin E and C, uric acid, flavonoids, and carotenoids) [19, 20]. The major pathological consequences associated with a dysfunctional redox system are often initiated by oxidative attacks on highly susceptible biomolecules (**Figure 1**). Polyunsaturated fatty acids, owing to their multiple double bonds, are especially vulnerable to peroxidation [21]. This process leads to the formation of lipid peroxides and secondary products such as malondialdehyde, which compromise membrane integrity by increasing rigidity, disrupting fluidity, and ultimately impairing normal cellular function [21, 22]. Similarly, reactive species can target the side chains of amino acids in membrane and cytosolic proteins, resulting in the formation of protein carbonyls. This oxidative modification alters protein structure and function, often leading to enzyme inactivation, loss of receptor activity, and disruptions in intracellular signalling pathways. Such changes can have widespread effects on cellular homeostasis and responsiveness [23]. Furthermore, free

radicals can induce damage to genetic material by modifying nitrogenous bases within DNA. These alterations can result in single- and double-strand breaks, base mispairing, and mutations [23, 24]. If not properly repaired, such genetic damage may accumulate and contribute to genomic instability, potentially triggering carcinogenesis and other long-term pathological conditions.

Inflammation: Mechanisms and regulation

Inflammation is a major evolutionarily conserved mechanism in the biological system in higher organisms that protects tissues against harmful stimuli such as microbial infection, physical injury, toxins, or other damaging conditions [5, 25]. Acute inflammation is a major component of the innate immune system, which acts as the body's first line of defense against invading pathogens and danger signals. Although inflammation has been generally associated with some classic symptoms such as pain, redness, and swelling for centuries, contemporary studies have demonstrated that inflammation entails a much more sophisticated molecular signal than what these visible symptoms suggest [26]. The initiation, progression, and resolution of the inflammatory response in the human system have been shown to involve a highly coordinated and regulated network of signaling pathways [27]. This regulation ensures effective defense against harmful stimuli without compromising normal cellular functions, as excessive and prolonged inflammatory responses can lead to severe pathological consequences. Immunocytes such as mast cells, macrophages, neutrophils, dendritic cells, and lymphocytes are key players in the detection of harmful agents as well as the coordination of immune responses. The type of inflammatory pathway activated by the innate immune system is largely determined by the type of stimulus involved [28, 29]. Bacterial infections are usually known to trigger the activation of specialized receptors, which stimulate the recruitment of inflammatory mediators such as cytokines and chemokines. These molecules facilitate pathogen elimination by increasing vascular permeability and promoting the recruitment of neutrophils and plasma proteins to the affected site [28, 29]. In some cases, which depend on the extent of injury and infection, inflammation can also produce systemic effects. Specifically, excess cytokines can stimulate the liver to produce acute-phase proteins, such as C-reactive protein and coagulation factors, which contribute to immune defense and systemic manifestations such as pain and fever through the production of prostaglandins. Viral infections activate a different pathway involving a distinct class of cytokines, e.g., type I interferons (IFNs), which stimulate antiviral proteins that inhibit viral replication [29, 30]. Instead, parasitic infections and allergic reactions often involve cytokines such as IL-4, IL-5, and IL-13, as well as histamine release [29, 31]. At the molecular level, inflammatory cascades begin when host cells detect harmful stimuli through specialized receptors (**Figure 2**) known as pattern recognition receptors (PRRs) [32]. These transmembrane receptors are expressed on immune and non-immune cells and are genetically programmed to recognize two conserved molecular patterns: Pathogen-associated molecular patterns, which originate from microbes, and damage-associated molecular patterns (DAMPs), produced by injured or stressed cells [32]. Some of the major classes of pattern recognition receptors identified so far include Nucleotide-binding Oligomerization Domain-like Receptors (NLRs), Toll-like receptors (TLRs), Calcium-dependent (C-type) lectin receptors (CLRs), and retinoic acid-inducible gene I-like receptors [33].

The activation of PRRs triggers intracellular signaling pathways that directly regulate specific gene expression in the nucleus. This leads to the synthesis of inflammatory mediators (cytokines and chemokines) [32, 34]. Some of these cytokines, such as interleukin-1 β (IL-1 β), are usually produced in an inactive form requiring additional processing before becoming active. This process occurs through the action of enzyme complexes known as inflammasomes, such as the NOD-like receptor family, pyrin domain-containing protein 1 (NLRP1), NLRP2, and NLRP3 inflammasome, which activate the protease caspase-1 to convert inactive precursor protein (pro-IL-1 β) into its functional form (IL-1 β) [35]. In response to viral infection, type I interferons initiate signaling cascades that facilitate the phosphorylation and nuclear localization of the IFN-stimulated gene factor 3 (ISGF3) complex, composed of signal transducers and activators of transcription 1 (STAT1), STAT2, and IFN-regulatory factor (IRF3) [29]. After translocation into the nucleus, this complex functions as

a transcriptional activator of interferon-stimulated genes, including protein kinase R (PKR) and 2',5'-oligoadenylate synthase (OAS). Protein kinase R is said to contribute to antiviral defense by suppressing protein synthesis and limiting the proliferation of infected cells, whereas OAS mediates the degradation of viral RNA, thereby impeding viral replication [29, 36]. In addition to the above, the activation of these receptors will also trigger activation of other signaling pathways through transcription factors such as MAPK, NF- κ B, activator protein-1 (AP-1), cyclic-AMP (cAMP) element binding protein (CREB), serum response factor (SRF), as well as Janus Kinase (JAK)-signal transducer pathways [34, 37].

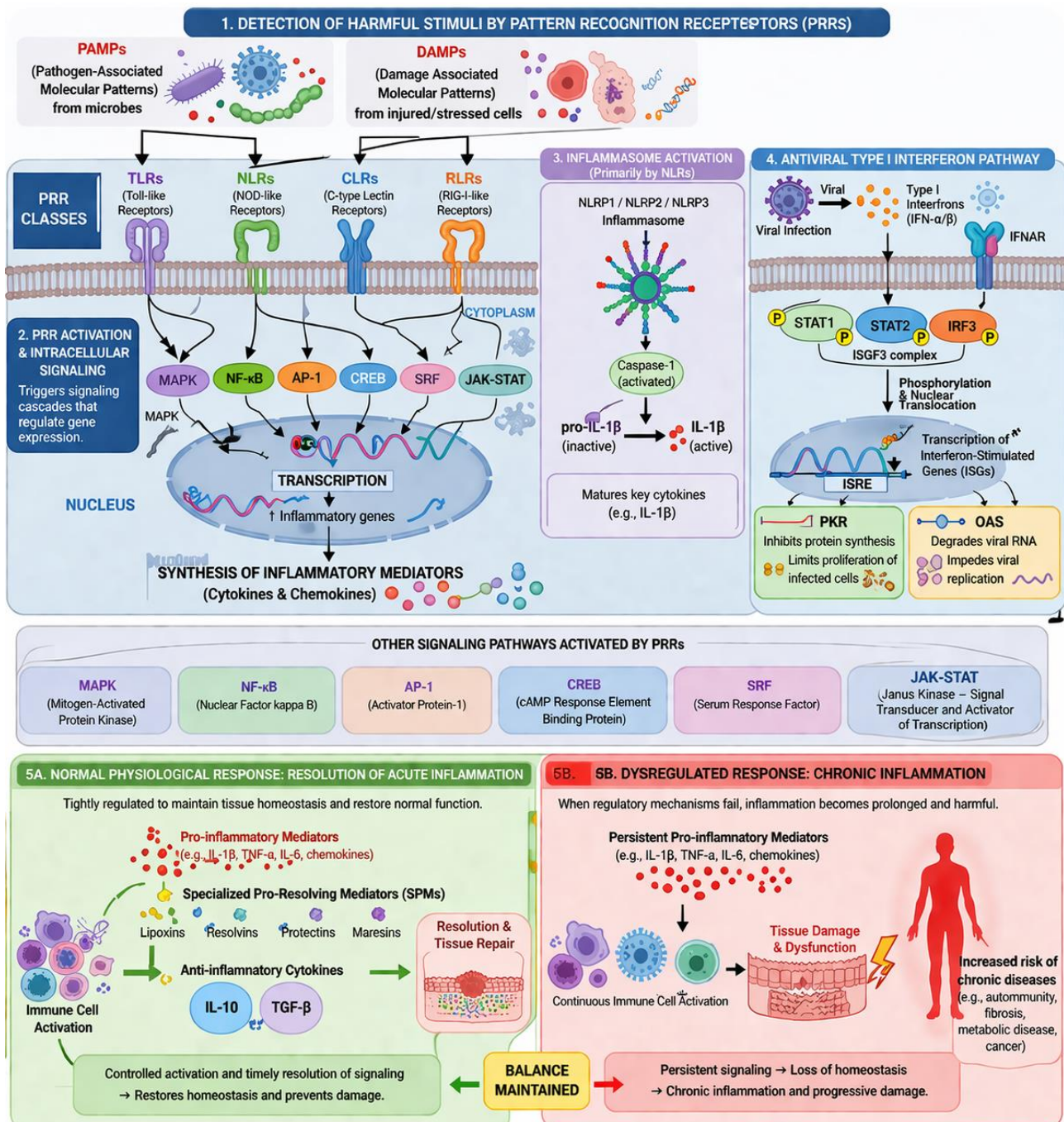


Figure 2: Molecular cascades in inflammatory signaling: From pattern recognition receptor activation to resolution and chronic inflammation

Pattern-recognition receptors (PRRs) detect pathogen-associated (PAMPs) and damage-associated (DAMPs) molecular patterns via TLRs, NLRs, CLRs, and RLRs, triggering intracellular signaling (MAPK, NF- κ B, AP-1, CREB, SRF, JAK-STAT) that drives transcription of inflammatory mediators. NLRP inflammasomes activate caspase-1 to process IL-1 β , while viral sensing induces type I interferon signaling through IFNAR-STAT1/STAT2/IRF3 to stimulate antiviral gene expression. These responses either resolve through anti-inflammatory and pro-resolving pathways restoring tissue homeostasis or, if dysregulated, lead to chronic inflammation, tissue damage, and increased risk of chronic disease.

Under normal physiological conditions, acute inflammation signals are usually tightly regulated to maintain tissue homeostasis and ensure quick restoration of normal body function following infection or injury. This controlled response involves a well-organized activation and timely resolution of inflammatory signaling pathways. This usually involves the recruitment of specialized pro-resolving mediators (SPMs), which may include lipoxins, resolvins, protectins, and maresins, together with the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor- β (TGF- β) [38, 39]. However, when regulatory mechanisms fail, the inflammatory response becomes dysregulated, resulting in prolonged exposure to the activities of these pro-inflammatory mediators and their pathways [40]. Such persistent signaling promotes homeostatic imbalance, continuous immune cell activation, and predisposition of the body's tissues to chronic inflammation and progressive damage.

Molecular interplay between oxidative stress and inflammation

Oxidative stress and chronic inflammation are two inseparable processes that are interconnected in a bidirectional manner, reinforcing each other through molecular networks propelled by redox imbalance, innate immune sensing, and downstream signaling amplification. The excessive cellular accumulation of reactive species (ROS/RNS), which disrupt cellular redox homeostasis and initiate direct molecular damage and immune activation, plays a major central role in the interplay of these processes [41]. As previously discussed, reactive species are generated from multiple enzymatic and organelle-based sources such as mitochondrial electron transport chains, NADPH oxidases (NOX), xanthine oxidase, and uncoupled nitric oxide synthases. Additionally, the activation of phagocytic cells (such as polymorphonuclear neutrophils (PMNs) and macrophages) during inflammatory responses has been proven to facilitate the release of large quantities of ROS through the upregulation of NOX activity, especially during respiratory burst [42]. At the same time, the formation of peroxynitrite, a highly reactive oxidant, through the reaction between superoxide radical and nitric oxide (formed through inducible nitric oxide synthase) further induces extensive biomolecular damage [43]. These reactive intermediates escalate lipid peroxidation, protein carbonylation, and DNA strand breaks, consequently leading to loss of membrane integrity, enzyme dysfunction, and genomic instability [44]. When the oxidative damage exceeds repair capacity, it leads to a critical mechanistic transition state that will lead to cellular stress responses and cell death (necrosis or late apoptosis). One major consequence of this is the release and accumulation of DAMPs, which serve as endogenous danger signals [45, 46]. Furthermore, the generation of oxidative-specific epitopes (OSEs), such as oxidized phospholipids, oxidized low-density lipoproteins (oxLDL), and oxidized cholesteryl esters, further increases immunological response, as these modified biomolecules can function as potent DAMPs, significantly enhancing their immunogenicity [7].

The recognition of these DAMPs by PRRs in the system leads to their activation and subsequent induction of intracellular signaling cascades, such as NF- κ B and MAPK pathways, resulting in transcriptional upregulation of pro-inflammatory cytokines, chemokines, and adhesion molecules (**Figure 3**). This will lead to the amplification of the inflammatory response via the promotion of leukocyte recruitment, endothelial activation, and increased vascular permeability. Among the DAMPs known, high mobility group box 1 (HMGB1) represents a central redox-sensitive mediator linking oxidative stress to inflammation [47]. HMGB1, known as amphoterin, is a highly conserved non-histone chromatin-associated protein across species. It can function as a non-histone protein and mediator of inflammatory response, depending on its cellular localization. Several studies have reported a strong link between the delocalization of HMGB1 from the nucleus to the cytoplasm and extracellular space and oxidative stress, usually through posttranslational modifications such as acetylation, reduction, ADP-ribosylation, methylation, and phosphorylation [48, 49]. Once modified through oxidative-mediated signals, HMGB1 is released passively from necrotic cells or actively secreted by activated immune cells. Extracellular HMGB1 interacts with PRRs such as TLR4 and RAGE, driving cytokine production, chemotaxis, dendritic cell maturation, and endothelial dysfunction [50]. Importantly, HMGB1 activity is strictly regulated by its redox state such that all-thiol (fully reduced) HMGB1 promotes chemotaxis

via chemokine interactions, whereas disulfide HMGB1 (partially reduced) induces cytokine release through TLR4 signaling. Alternatively, fully oxidized HMGB1 is functionally inactive and associated with immune tolerance [51, 52]. Thus, the oxidative microenvironment not only governs HMGB1 release but dictates its immunological function, effectively acting as a molecular switch between immune activation and resolution.

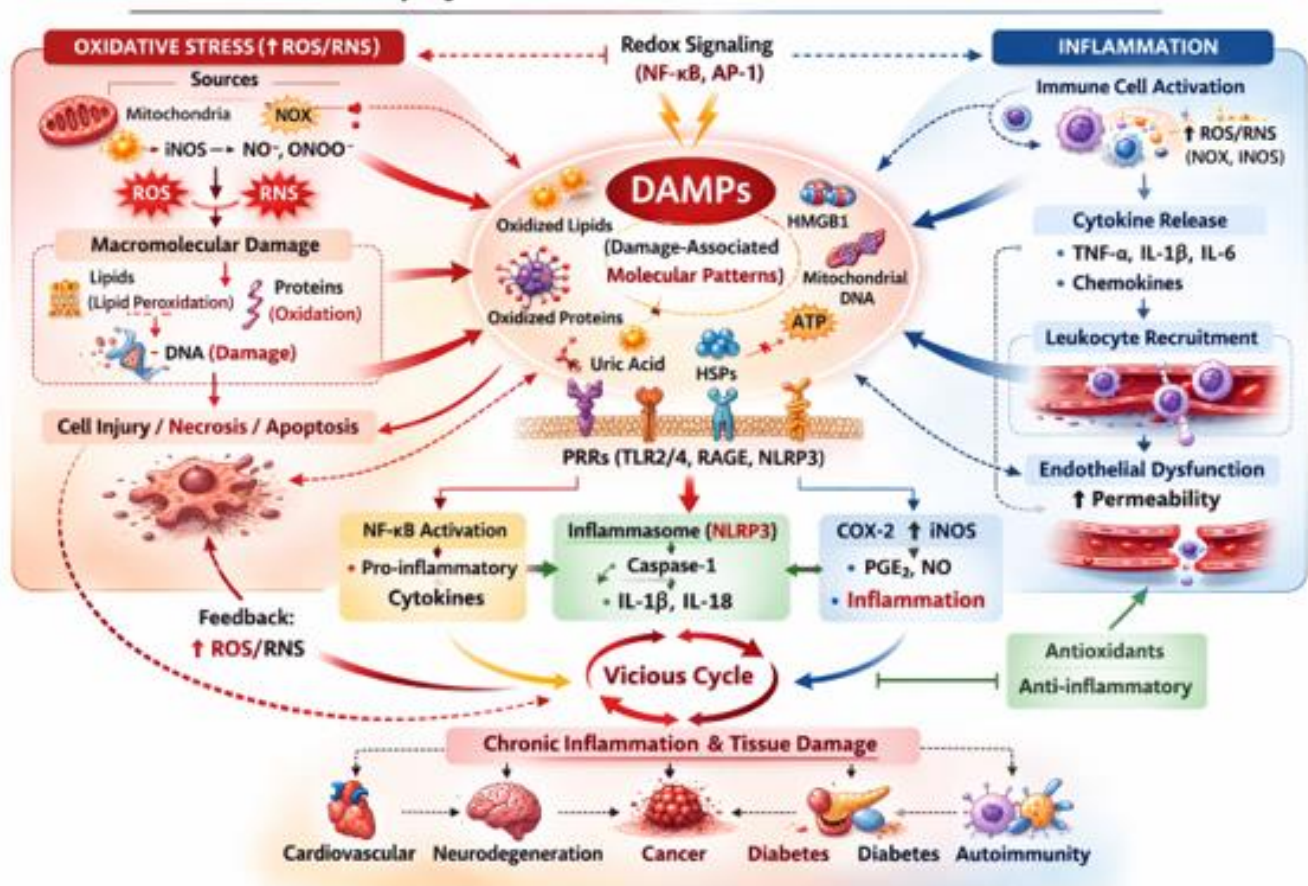


Figure 3: Interplay between oxidative stress, DAMP-mediated PRR activation, and feed-forward inflammatory signaling in chronic disease pathogenesis

Oxidative stress, driven by excess ROS/RNS from mitochondrial and enzymatic sources (e.g., NOX, iNOS), induces lipid peroxidation, protein oxidation, and DNA damage, leading to cell injury, necrosis, or apoptosis. These events generate and release DAMPs (including oxidized lipids/proteins, HMGB1, mitochondrial DNA, ATP, uric acid, and HSPs), which engage PRRs (TLR2/4, RAGE, NLRP3) and activate redox-sensitive signaling pathways (NF-κB, AP-1). The hallmark is the production of proinflammatory cytokines, NLRP inflammasome activation, and other events, including the induction of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) as well as the production of PGE₂ and NO. Moreover, immune cell activation amplifies ROS/RNS generation, promoting cytokine release, chemokine-driven leukocyte recruitment, and endothelial dysfunction with increased permeability. These interrelated signals establish a self-perpetuating cycle between oxidative stress and inflammation that drives chronic inflammation, tissue damage, and progression of cardiovascular, neurodegenerative, metabolic, neoplastic, and autoimmune diseases, with partial modulation by antioxidant and anti-inflammatory mechanisms.

At the same time, oxidative stress can also trigger the activation of intracellular danger-sensing complexes such as the NLRP3 inflammasome. NLRP3 is an intracellular receptor that forms a multiprotein inflammasome complex through its interaction with the apoptosis-associated speck-like protein (ASC), leading to the recruitment and activation of procaspase-1 [53]. The activation of the NLRP3 inflammasome has been reported to be closely linked to cellular redox status via its association with the thioredoxin-interacting protein (TXNIP). Under basal conditions, TXNIP is usually associated with thioredoxin (Trx); however, elevated intracellular ROS levels promote the dissociation of TXNIP from Trx [54]. Upon its liberation, TXNIP binds to NLRP3, facilitating inflammasome assembly and activation of caspase-1 and subsequent maturation of IL-1β and IL-18. This pathway represents a critical link between redox imbalance and innate immune amplification, further propagating inflammatory signaling [55].

The interplay becomes cyclical as inflammation itself reinforces oxidative stress. Activated immune cells sustain high ROS/RNS production via NOX and iNOS, while pro-inflammatory mediators further enhance oxidative enzyme expression. Moreover, DAMPs such as HMGB1 can directly induce ROS generation, creating a feed-forward loop [56, 57]. This establishes a vicious cycle characterized by persistent ROS/RNS production, continuous DAMP release, sustained PRR activation, and persistent cytokine signaling. This amplification loop underlies the progression from acute, controlled inflammation to chronic inflammatory states associated with tissue injury and disease [58]. At the tissue level, the continuous interplay and signal amplifications further contribute to endothelial dysfunction, increased vascular permeability, leukocyte infiltration, and progressive extracellular matrix degradation. All these processes contribute to the pathogenesis of multiple disorders, including cardiovascular diseases, neurodegenerative conditions, cancer, diabetes, and chronic inflammatory lung diseases [58].

Chronic diseases linked to the nexus

Neurodegenerative: Neurodegenerative disorders encompass several disorders of the central nervous system characterized by progressive damage and decline in the activities of neurons and cognitive dysfunctions. Examples of such disorders include Multiple sclerosis, Alzheimer's, Huntington's, and Parkinson's disease. They are characterized by different molecular features such as beta-amyloid plaque accumulation in the brain (Alzheimer's disease), Lewy body formation (Parkinson's disease), and genetic complications (Huntington's disease) [59, 60]. Evidence from both experimental models and human studies has revealed that the oxidative stress-inflammatory nexus is the major driver in the pathophysiology of these neurodegenerative diseases [61, 62]. The brain's high metabolic rate and reliance on mitochondrial function make it particularly susceptible to oxidative damage [63]. Numerous studies have reported crosslinks between increased oxidative markers and early neuronal injury in conditions such as Alzheimer's and Parkinson's diseases [64]. Oxidative stress has been shown to promote protein misfolding and aggregation, a key pathological feature in these disorders. At the same time, increased oxidative signals can also activate microglia, resident macrophage cells which serve as the brain's resident immune cells [8]. As discussed earlier in this review, acute microglial activation may be protective; however, chronic activation is now widely recognized as a contributor to disease progression, as it sustains the release of pro-inflammatory cytokines and reactive species. Furthermore, sustained oxidative and inflammatory stress can compromise the integrity of the blood-brain barrier, allowing peripheral immune components to enter the central nervous system. Interestingly, growing evidence has indicated that disruption of the blood-brain barrier is a critical event in neurodegeneration [65, 66].

Cardiovascular disorders: Pathophysiological disorders related to blood vessels and the heart are another major group of diseases of concern in human society. A substantial body of research has identified oxidative stress and chronic inflammation as central, interdependent drivers of cardiovascular disease [67]. Oxidative stress contributes to endothelial dysfunction, promotes atherogenesis and plaque development, while inflammatory processes destabilize plaques, increasing the risk of rupture and subsequent thrombosis [68]. The connection between oxidative stress and inflammation in cardiovascular diseases becomes clear very early on, particularly through damage to the inner lining of blood vessels (the endothelium) [69]. The inner lining under normophysiological conditions is responsible for the regulation of blood flow and ensuring the smooth functioning of the vessels. However, the overload of reactive oxygen species in endothelial cells has been reported to reduce the bioavailability of nitric oxide (NO), thereby impairing vasodilation [70, 71].

Oxidative stress promotes the oxidation of circulating low-density lipoprotein (LDL), giving rise to the accumulation of Oxidized LDL. Studies have shown that Ox-LDL promotes vascular inflammation by inducing monocyte chemoattractant protein-1 (MCP-1) and adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, facilitating monocyte adhesion and subendothelial infiltration [72-75]. It can further stimulate endothelial production of

macrophage colony-stimulating factor, driving monocyte differentiation into macrophages [76]. Although oxidized LDL can induce apoptosis in various cell types, it accumulates within macrophages to form foam cells, which secrete pro-inflammatory cytokines and amplify oxidative stress, establishing a self-perpetuating cycle that promotes atheroma formation and progression to cardiovascular events [72, 74]. Lipid oxidation products such as lysophosphatidylcholine have also been reported to impair nitric oxide synthesis, reducing its bioavailability [77]. Thus, oxidized LDL plays a central role in the initiation, maintenance, and progression of atherosclerosis. Its effects are largely mediated by Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a scavenger receptor minimally expressed in normal vessels but markedly upregulated in endothelial cells, vascular smooth muscle cells, and macrophages within atherosclerotic lesions in response to cytokines and shear stress [78, 79]. Oxidative imbalance has also been reported to promote the development of arterial hypertension, while also triggering inflammatory responses, fibrotic remodeling, and apoptotic cell death. In fact, studies have shown that excessive ROS can activate hypertrophic signaling pathways, disrupt myocardial calcium (Ca^{2+}) homeostasis, and facilitate the progression of atherosclerotic plaque formation [80].

Diabetes mellitus and metabolic disorders: The persistent hyperglycemic condition, which is the hallmark of diabetes mellitus, has been shown both in mechanistic and clinical studies to enhance reactive oxygen species production through mitochondrial overactivity, polyol pathway, and non-enzymatic glycation processes [81-83]. The interplay of oxidative and inflammatory stress has long been established by scientific literature both in the initiation and secondary complications of diabetes mellitus. One of the major pathways of concern is the formation of advanced glycation end products and their interaction with specific receptors (RAGE). Studies have shown that this signaling pathway can amplify inflammatory responses while simultaneously increasing oxidative stress, creating a self-sustaining cycle of cellular injury as discussed earlier [84, 85]. Oxidative stress and inflammation act synergistically to impair insulin signaling and metabolic regulation, partly through the activation of stress kinases such as c-Jun N-terminal kinase (JNK) and the inhibitor of nuclear factor- κ B (I κ B) kinase (IKK), which inhibit insulin receptor substrate-1 (IRS-1) [86-88]. These factors have also been reported to have negative effects on adipose tissues via the suppression of the expression and secretion of adiponectin by fat cells, complicating insulin resistance [89]. Furthermore, the continuous oxidative-inflammatory burden in diabetic conditions is the major contributing factor to the development of various secondary complications, particularly microvascular damage affecting the kidneys, nerves, and retina [90]. In diabetic nephropathy, for example, prolonged hyperglycemic conditions have been reported to cause renal hypoxia as well as altered tubulo-glomerular feedback.

Conclusion: The mutual reinforcement between oxidative stress and inflammation constitutes a critical mechanistic framework underlying the pathogenesis of numerous human diseases. Reactive oxygen species and inflammatory mediators form a self-propagating cycle that drives cellular damage, dysregulated signaling, and loss of tissue integrity and functions. From the molecular perspective, this interplay involves redox-sensitive signaling pathways, mitochondrial dysfunction, and pro-inflammatory mediators, collectively contributing to various health issues such as cardiovascular, metabolic, and neurodegenerative diseases. Consequently, therapeutic strategies should focus on restoring redox balance rather than complete suppression of reactive oxygen species. Targeting oxidative stress and inflammation remains a promising approach; however, molecular precision and pathway-specific interventions are still needed to effectively mitigate disease while preserving normal cellular function.

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